11. RISK CHARACTERIZATION

11.1. INTRODUCTION

The U.S. Environmental Protection Agency (EPA) first published a health assessment of 1,3-butadiene in 1985. The 1985 assessment concluded that 1,3-butadiene was a possible human carcinogen and calculated an upper bound cancer potency estimate of 0.25/ppm based on mouse data. Since then, a number of new studies on 1,3-butadiene have been completed in various disciplines such as epidemiology, toxicology, and pharmacokinetics. The purpose of this effort was to review the new information and determine if any changes were needed to the earlier conclusions.

This reassessment is intended to serve as a source document for risk assessors inside and outside the Agency. Its development, however, was prompted primarily by a request from EPA's Office of Mobile Sources (OMS) to support decision making regarding the Air Toxic Rule's Section 202 (l) (2) of the Clean Air Act Amendment. The scope of the document has been limited to address only the health effects specifically requested by OMS: carcinogenicity, mutagenicity, and reproductive/developmental toxicity. Similarly, a detailed exposure assessment was not requested and not conducted. For background purposes, however, some exposure information has been included.

The major findings of this report are as follows. First, sufficient evidence exists to consider 1,3-butadiene a known human carcinogen. The evidence for this includes findings in epidemiologic studies as well as clear evidence that 1,3-butadiene is an animal carcinogen and is metabolized into genotoxic metabolites by experimental animals and humans.

Second, based on linear modeling of human data, the best estimate of lifetime extra cancer risk from continuous 1,3-butadiene exposure is about 9×10^{-3}/ppm, or 9×10^{-6}/ppb. In other words, it is estimated that 9 persons in 1 million exposed to 1 ppb 1,3-butadiene continuously for their lifetimes would develop cancer as a result of their exposure. Lower cumulative exposures are expected to result in risks that are proportionately lower.

Third, although there are no human data on reproductive or developmental effects, a variety of such effects have been observed in mice and rats exposed to 1,3-butadiene. A reproductive/developmental reference concentration (RfC) of 0.05 ppb was calculated based on the critical reproductive effect of reduced litter sizes, reflecting increased prenatal mortality, observed among the offspring of male mice exposed to 1,3-butadiene.

Fourth, there are insufficient data to determine if children or other special subpopulations are differentially affected by exposure to 1,3-butadiene. Heavy smokers are likely to be more heavily exposed than the general population.

This chapter will briefly summarize and integrate the critical data and analyses on which these findings are based and discuss the strengths and weaknesses of those data and the resulting confidence in the findings. With the exception of the section on special subpopulations, all of the sections in this chapter discuss material presented in the earlier chapters of this assessment.

11.2. EXPOSURE OVERVIEW

Approximately 3 billion pounds of 1,3-butadiene are produced annually in the United States. 1,3-Butadiene is used primarily in the manufacture of styrene-butadiene rubber, plastics, and thermoplastic resins. Environmental releases occur from process vents during these operations. 1,3-Butadiene is not a component of gasoline or diesel fuel, but is formed as a by-product of incomplete combustion. Mobile sources, including both on-road and nonroad engines, are estimated to account for 79% of all 1,3-butadiene emissions (EPA, 1992). 1,3-Butadiene emissions from vehicles are reduced by catalytic converters; total emissions may decline as older cars without converters are removed from service.

The compound is highly volatile and slightly soluble in water. Thus, environmental releases result primarily in emissions to the atmosphere. In the atmosphere, 1,3-butadiene undergoes rapid destruction by photoinitiated reactions, and 50% of it is removed in approximately 6 hours (U.S. DHHS, 1992). Although it is degraded rapidly in the atmosphere, 1,3-butadiene is almost always present at low concentrations in urban and suburban areas. Because of this, the general population is exposed to some levels via inhalation. 1,3-Butadiene is not found in significant amounts in food, soil, water, plants, fish, or sediment. Therefore, the predominant pathway of exposure is via inhalation.

Monitoring done from 1987 to 1994 by Aerometric Information Retrieval System at more than 20 different urban and suburban locations detected ambient air levels of 1,3-butadiene ranging from 0.22 to 1.02 $\mu g/m^3$ (0.10 to 0.46 ppb). Indoor air levels are likely to be higher than ambient levels when smoking occurs. 1,3-Butadiene emissions from cigarettes have been measured to be 200 to 400 µg/cigarette, and levels in smoke-filled bars have been found to range from 2.7 to 19 $\mu g/m^3$ (1.2 to 8.4 ppb) (Lofroth et al., 1989; Brunnemann et al., 1990).

11.3. CANCER HAZARD ASSESSMENT

11.3.1. Human Evidence

Sufficient evidence exists to consider 1,3-butadiene a known human carcinogen.

In most situations, epidemiologic data are used to delineate the causality of certain health effects. Several cancers have been causally associated with exposure to agents for which there is no direct biological evidence. Insufficient knowledge about the biological bases for diseases in humans makes it difficult to identify exposure to an agent as causal, particularly for malignant

diseases when the exposure was in the distant past. Consequently, epidemiologists and biologists have provided a set of criteria supportive of a causal relationship between an exposure and a health outcome. A causal interpretation is enhanced for studies that meet these criteria. None of these criteria actually proves causality; actual proof is rarely attainable when dealing with environmental carcinogens. None of these criteria should be considered either necessary (except temporality of exposure) or sufficient in itself. The absence of any one or even several of these criteria does not prevent a causal interpretation. However, if more criteria apply, it provides credible evidence for causality. The following discussion addresses the strengths and limitations of the epidemiologic studies of workers occupationally exposed to 1,3-butadiene, from which the human evidence is derived, and then summarizes how adequately the causality criteria apply.

The conclusion of "sufficient evidence" of human carcinogenicity is based on more than 10 epidemiologic studies examining five different groups of workers. These studies are summarized in Table 11-1.

The strongest evidence comes from the follow-up study of a cohort of 15,000 synthetic rubber workers (UAB cohort) conducted by Delzell et al. (1996) and Macaluso et al. (1996) and reported in two components. The cohort was derived from seven U.S. plants and one Canadian plant. The follow-up was from 1943 to 1994. Investigators estimated the exposures to 1,3-butadiene, styrene, and benzene for each worker (Macaluso et al., 1996). Quantitative exposures were calculated and limited validation of exposure estimates were attempted by various means. Cumulative and peak exposures were calculated for each worker. Comparison with the U.S. population resulted in significant excesses for leukemia in ever-hourly workers (43% higher than general population) and its subcohort of blacks (127%) (Delzell et al., 1996). Significant excesses were also found in the ever-hourly subcohort for year of death (87% for 1985+), year of hire (100% for 1950-59), age at death (79% for <55 years), and for more than 10 years employment and more than 20 years since hire (92% for whites and 336% for blacks). Laboratory workers, maintenance workers, and polymerization workers also showed higher risks of 331%, 165%, and 151%, respectively. All these analyses were conducted adjusting for styrene and benzene. When internal comparison was carried out using the estimated ppm-years
exposure data, risk ratios increased with increasing exposures. These findings demonstrate specificity and strength of association. A fairly consistent association between exposure to butadiene and occurrence of leukemia across the plants was also found. Furthermore, the trend test for increasing risk of leukemia with increasing exposure to 1,3-butadiene was statistically significant (dose response).

The major strengths of this study are as follows. First, the study had detailed and comprehensive quantitative exposure estimations for 1,3-butadiene, styrene, and benzene for

Table 11-1. Summary of epidemiologic studies

Plants	Number of workers, dates studied	Authors	Approach	Significant findings
7 U.S. and 1 Canadian polymer production plants (UAB cohort)[a]	15,000, 1943-1994	Delzell et al., 1996 Macaluso et al., 1996	Cohort study using quantitative exposure estimates for each worker	Excess mortality due to leukemia; leukemia risk increased with increasing exposure level
7 U.S. and 1 Canadian polymer production plants (JHU cohort)[a]	13,500, 1943 - 1985	Matanoski and Schwartz, 1987 Matanoski et al., 1989, 1990, and 1993 Santos-Burgoa et al., 1992	Cohort studies using qualitative exposures; case-control study using estimated quantitative exposures for each case and control	Excess mortality due to lumpho- hematopoietic cancers; leukemia risk increased with increasing exposure level in case-control study
1 U.S. monomer production plant (Texaco cohort)	2,800, 1943-1994	Downs et al., 1987 Divine, 1990 Divine et al., 1993 Divine and Hartman, 1996	Cohort studies using qualitative exposures, last study made quantitative exposure estimates	Excess mortality due to lymphosarcoma in prewar workers
3 U.S. monomer production plants (Union Carbide cohort)	364, 1940-1990	Ward et al., 1995 and 1996a	Cohort study using qualitative exposures	Excess mortality due to lymphosarcoma in World War II workers
1 U.S. monomer production plant (Shell Oil Deer Park cohort)	614, 1948-1989	Cowles et al., 1994	Cohort study using qualitative exposures	No increase in mortality or morbidity

[a]Six U.S. plants and one Canadian plant were common in Johns Hopkins University (JHU) and University of Alabama, Birmingham (UAB) studies.

each individual. Second, the cohort was large, with a long follow-up period of 49 years. Third, both external and internal comparison showed similar results. Fourth, adjustments for potential confounding factors were carried out. Fifth, analyses by duration of employment and for latency were conducted.

The study had some limitations. First, some misclassification of exposure may have occurred with respect to certain jobs, but it is unlikely to have occurred only in leukemia cases, because the exposures were calculated *a priori* to health effects evaluation. Second, the excess mortality observed for leukemia was based on death certificates and was not verified by medical records. This may have resulted in some misclassification of leukemias. Third, histologic typing of leukemia was also not available. Thus, currently it is not known whether a single cell type or more than one cell type is associated with the exposure to 1,3-butadiene.

A large cohort of synthetic rubber workers (JHU cohort)[1], assembled from one Canadian and seven U.S. plants, was also studied by Matanoski and Schwartz (1987) and then followed up by Matanoski et al. (1989, 1990). The follow-up included a nested case-control study (Santos-Burgoa et al., 1992). Approximately 13,500 individuals were followed from 1943 to 1985. A significant excess of lymphohematopoietic cancer was observed in the cohort study. The nested case-control study from this cohort, comprising 59 cases of lymphohematopoietic cancers and 193 matched controls, found significantly increased relative odds for leukemia. Increases of 7 times in the high-exposure group and of 4 times in the low-exposure group were observed in the ever/never exposed analysis, of 9 times in the matched analysis, and of 8 times in the conditional analysis (specificity and strength of association). Exposures to 1,3-butadiene and styrene were estimated for each case and control using job records and levels of exposures to 1,3-butadiene and styrene associated with those jobs, independently of the case or control status. A significant trend of increasing risk of leukemia with increasing exposure level of 1,3-butadiene was also observed (dose response).

The findings of excess leukemia risk in the nested case-control study were questioned by Acquavella (1989) and Cole et al. (1993), as these findings were inconsistent with the absence of excess leukemia risk in the base cohort study. Thus, Matanoski et al. (1993) reevaluated the original nested case-control study by choosing a new set of three controls per case. The investigators also verified the cause of death by obtaining the hospital records (25 out of 26 were correctly recorded on the death certificates). The findings of the new analysis were similar to those of the earlier analysis. Although the controversy about the cohort and case-control study is still not resolved, the nested case-control study demonstrates a strong association between exposure to 1,3-butadiene and occurrence of leukemias.

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[1] One Canadian plant and six U.S. plants were common in the JHU and UAB studies.

The main strengths of the JHU cohort study are as follows. First, this was the first large cohort study of polymer production workers. Second, adjustments for confounding exposures were conducted. Third, analyses by duration of employment and for latency were carried out. Fourth, the nested case-control study was well conducted and well analyzed, with quantitative estimation of exposures for each case and control as well as verification of leukemia.

Limitations of the JHU cohort study included the exclusion of more than 50% of the population because of the lack of work histories, work start date, and exposure data. In addition, the follow-up for four plants, where the starting date was 1957 to 1970, may not have been long enough for malignancies to develop. As far as the nested case-control study is concerned, the estimated exposures were crude and not substantiated by air monitoring data. Exposure misclassification may have occurred based on the estimated exposures by job if the jobs were incorrectly identified for higher or lower exposure. However, the panel members were blind toward the status of cases and controls; thus, the distribution of misclassification should be the same in cases and controls.

Three different cohorts of monomer production workers were studied. The largest cohort of approximately 2,800 workers in a Texaco plant followed from 1943 to 1994 by several investigators (Downs et al., 1987; Divine, 1990; Divine et al., 1993; Divine and Hartman, 1996). All the investigations essentially found lower than expected mortality from all causes and total cancers as compared to the general population. The only significant excess mortality observed was for lymphosarcoma in the prewar subcohort of workers who had worked for less than 10 years and had a latency of 0-9 years; 154% to 169% higher than the general population. Even though exposures were estimated in the last follow-up, no information about exposure levels was available for the prewar period; however, it is believed that exposures were high.

The major strengths of this study are, first, it is the largest cohort of monomer workers. Second, it had a long follow-up period of 52 years. Third, analyses by duration of employment, and for latency, as well as adjustment for potential confounding factors were conducted. Fourth, the exposures in each individual were estimated in the last follow-up.

The main limitation was lack of exposure information in the earlier follow-ups. Furthermore, although the investigators estimated the exposures for each individual in their last follow-up, no information was available on work histories or levels of 1,3-butadiene exposure during the prewar period, which made exposure estimation in the prewar workers impossible.

A small cohort of 364 individuals who had potential exposure to 1,3-butadiene at three Union Carbide plants during World War II was studied by Ward et al. (1995, 1996a). This investigation also found a statistically significant excess for lymphosarcoma by 477%, which was based on four cases (specificity and strength of association). The observation of excess lymphosarcoma was consistent with the finding in the Texaco cohort study. The main limitations

of this study are that the cohort was small and that exposures were assumed based on job categories. In addition, there was no analysis for latency or adjustments for potential confounding by exposure to other chemicals.

Cowles et al. (1994) studied the third cohort of 614 workers. This study failed to show any increased mortality or morbidity. Due to several methodologic limitations such as lack of exposure information, short follow-up, and lack of information on confounders, this study failed to provide any negative evidence toward the causal association between exposure to 1,3-butadiene monomer and occurrence of lymphosarcoma that was observed in the other two studies.

All the epidemiologic studies, cohort and nested case-control, evaluated for this assessment are observational studies in occupationally exposed populations. As such, they have various methodologic strengths and limitations as discussed above. A common limitation to all the studies is the use of death certificates, which could lead to misclassification bias. Validation of diagnosis of lymphohematopoietic cancer was not done in any of the studies except in Matanoski et al. (1993). This is a methodologic concern, given the fact that lymphohematopoietic cancer recording on death certificates is unreliable (Percy et al., 1981).

Based on these monomer and polymer production workers' cohorts, it is obvious that an increased number of lymphohematopoietic cancers is observed in these populations. A clear difference is becoming apparent, though. Increased lymphosarcomas develop in monomer workers, whereas excess leukemias occur in polymer workers. Furthermore, the lymphosarcomas observed in the monomer workers were among wartime workers, who were probably exposed to higher levels of 1,3-butadiene for shorter periods of time and not in long-term workers with low levels of exposure. A similar observation comes from the stop-exposure studies conducted by Melnick et al. (1990c). They observed that for a given total exposure, the incidence of lymphoma was greater among mice exposed to higher concentrations of butadiene for a shorter period of time (625 ppm for 26 weeks) than among mice exposed to a lower concentration for a longer period of time (312 ppm for 52 weeks). Consequently, this suggests that it may be the concentration of 1,3-butadiene rather than the duration of exposure that is important in the occurrence of lymphomas. There is a null relationship between exposure to 1,3-butadiene monomer and occurrence of leukemias, which are observed in polymer workers. This may be due to the exposure patterns for 1,3-butadiene in monomer production workers or to the absence of exposure to a necessary co/modifying factor or a confounding factor that occurs in polymer production workers. Data are currently lacking to confirm or refute any of these possibilities. The findings of the UAB study, which investigated styrene and benzene exposures as well, suggest that the observed associations of leukemia with 1,3-butadiene exposure are not due to

confounding by exposure to other chemicals. The findings of excess leukemias in polymer production workers are consistent with a causal association with exposure to 1,3-butadiene.

Table 11-2 shows the application of the causality criteria to the studies discussed above.

As these criteria are well satisfied, it is concluded that there is sufficient evidence to consider 1,3-butadiene a known human carcinogen.

11.3.2. Animal Data

***1,3-Butadiene is an animal carcinogen*.**

Chronic bioassay studies provide unequivocal evidence that 1,3-butadiene is a multisite carcinogen in both rats and mice. These studies also demonstrate that the mouse is more sensitive than the rat to 1,3-butadiene-induced carcinogenicity and develops tumors at different sites, although the reasons for these interspecies differences are not understood at this time. The most sensitive site was the female mouse lung, which exhibited significantly increased tumor incidence at the lowest exposure concentration tested (6.25 ppm).

Table 11-2. Epidemiologic causality criteria

Criteria	Monomer plant workers	Polymer plant workers
Temporality: exposure occurred prior to effect	Yes	Yes
Specificity of cancer	Lymphosarcoma	Leukemia (specific cell type[s] not known at this time)
Strength of association	154% to 477% higher mortality from lymphosarcoma than general population	7 to 9 times higher relative odds for leukemia (nested case-control study)[a]; 151% to 331% higher mortality from leukemia than general population
Consistency	2 of 3 studies agree	Fairly consistent across the plants
Dose-response relationship	Cannot be demonstrated due to lack of quantitative exposure data	Yes
Biological plausibility	Yes	Yes

[a] Relative odds is the ratio of the frequency of exposure to 1,3-butadiene in cases to the frequency of exposure to 1,3-butadiene in controls, where both the cases and controls are from the same occupational cohort.

11.3.3. Other Supportive Data

1,3-Butadiene is metabolized into genotoxic metabolites by experimental animals and humans.

Metabolic activation is required for 1,3-butadiene carcinogenicity, and there is evidence that 1,3-butadiene is metabolized to at least three genotoxic metabolites: a monoepoxide (1,2-epoxy-3-butene, EB), a diepoxide (1,2:3,4-diepoxybutane, DEB), and an epoxydiol (3,4-epoxy-1,2-butanediol). The enzymes responsible for the metabolic activation of 1,3-butadiene to these epoxide metabolites exist in humans as well as mice and rats. EB and DEB have been measured in the blood of rats, mice, and monkeys after 1,3-butadiene exposure, and their production by human tissues has been observed in vitro. Formation of 3,4-epoxy-1,2-butanediol has been observed in vitro using tissues from mice, rats, and humans. Activation rates for 1,3-butadiene are typically higher in the mouse than in the rat, reflected by higher tissue concentrations of EB and DEB in the mouse versus the rat. Activation rates in humans exhibit a high degree of variability and appear to span the range between mice and rats.

Among the genotoxic effects of 1,3-butadiene is an N^7-alkylguanine adduct that has been observed in the liver DNA of exposed mice and in the urine of an exposed worker. Similarly, increased frequencies of *hprt* mutations have been observed in the lymphocytes of mice and rats exposed to 1,3-butadiene and in lymphocytes of occupationally exposed workers. Even though these mutations may not be directly related to tumor development, they provide in vivo evidence of similarities in the disposition and genotoxic action of 1,3-butadiene between mice and humans.

11.3.4. Cancer Characterization

1,3-Butadiene is a known human carcinogen.

This characterization is supported by the three findings discussed above: (1) epidemiologic studies showing increased leukemias in workers occupationally exposed to 1,3-butadiene (by inhalation), (2) laboratory studies showing that 1,3-butadiene causes a variety of tumors in mice and rats by inhalation, and (3) studies demonstrating that 1,3-butadiene is metabolized into genotoxic metabolites by experimental animals and humans. The specific mechanisms of 1,3-butadiene-induced carcinogenesis are unknown; however, it is virtually certain that the carcinogenic effects are mediated by genotoxic metabolites of 1,3-butadiene. Under EPA's 1986 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986), 1,3-butadiene would be classified as a "Group A"—Human Carcinogen. It is characterized as a "Known Human Carcinogen" according to EPA's 1996 *Proposed Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1996).

11.4. QUANTITATIVE RISK ESTIMATION FOR CANCER

Lifetime extra cancer risk is estimated to be about 9×10^{-3} per ppm continuous 1,3-butadiene exposure, based on human data.

The Delzell et al. (1995) retrospective cohort study of more than 15,000 male styrene-butadiene rubber production workers provides high-quality epidemiologic data for estimating the human cancer risk from 1,3-butadiene exposure. In the Delzell et al. study, 1,3-butadiene exposure was estimated for each job and work area for each study year, and these estimates were linked to workers' work histories to derive cumulative exposure estimates for each individual worker. Consistent with EPA's 1986 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986) and evidence of the genotoxicity of 1,3-butadiene, the linear relative rate exposure-response model reported by Delzell et al. was used to calculate a maximum likelihood estimate (MLE) of 8.7×10^{-3}/ppm (or 9×10^{-3}/ppm, rounded to one significant figure) for lifetime extra risk of leukemia mortality from continuous environmental 1,3-butadiene exposure. The corresponding 95% upper limit on unit risk is 0.02/ppm. There were insufficient exposure-response data to calculate a lymphoma risk estimate from the monomer cohorts.

Alternatively, interpreting the proposed new carcinogen risk assessment guidelines (U.S. EPA, 1996), linear extrapolation from the LEC_{01} or the EC_{01} (i.e., the 95% lower confidence limit or MLE, respectively, of the exposure concentration associated with a 1% increased risk) is warranted given the clear genotoxicity of 1,3-butadiene and the fact that a 1% increase in risk is within the range of the epidemiology data. The models presented by Delzell et al. yield LEC_{01} and EC_{01} values ranging from 0.066 to 0.64 ppm and from 0.45 to 1.16 ppm, respectively. The corresponding cancer potency estimates range from 0.016/ppm to 0.15/ppm (based on the LEC_{01}) and from 8.7×10^{-3}/ppm to 0.022/ppm (based on the EC_{01}). The square root model provided the best fit to the data and was chosen by Delzell et al. for further refinements. Thus, their final square root model might be the appropriate model to select for determination of the ultimate "point of departure" for linear extrapolation. Based on this model, a cancer potency estimate of 0.08/ppm is obtained from the LEC_{01} of 0.12 ppm, and a potency estimate of 0.02/ppm is obtained from the EC_{01} of 0.45 ppm. These unit risk estimates are roughly two- and fourfold higher, respectively, than the MLE and upper bound estimates calculated using the linear model described above.

For comparison purposes, human unit cancer risk estimates based on extrapolation from the results of lifetime animal inhalation studies are summarized in Table 11-3. These potency estimates are 95% upper confidence limits on unit cancer risk calculated from incidence data on all significantly elevated tumor sites using a linearized low-dose extrapolation model. Such estimates are generally considered by EPA to represent plausible upper bounds on the extra unit cancer risk to humans. Table 11-3 also includes unit risk estimates based only on the

Table 11-3. Estimates of upper bounds on human extra unit cancer risk (potency) from continuous lifetime exposure to 1,3-butadiene based on animal inhalation bioassays

Species	Sex	Tumor sites/types	Upper bound on potency (ppm^{-1})
Rat[a]	M	Leydig cell, pancreatic exocrine cell, Zymbal gland	4.2×10^{-3}
	F	Mammary gland, thyroid follicular cell, Zymbal gland	5.6×10^{-2}
Mouse[b]	M	Lymphocytic lymphomas, histiocytic sarcomas, heart hemangiosarcomas, lung, forestomach, Harderian gland, liver, preputial gland	0.22
	F	Lymphocytic lymphomas, heart hemangiosarcomas, lung, forestomach, Harderian gland, liver, ovary, mammary gland	0.29
	M	Lymphocytic lymphomas	6.4×10^{-3}
	F	Lymphocytic lymphomas	2.4×10^{-2}

[a] From U.S. EPA's 1985 assessment; linearized multistage model.
[b] Based on 1993 NTP study; Weibull multistage time-to-tumor model.

lymphocytic lymphomas in mice, because this was the tumor type in rodents most analogous to the lymphohematopoietic cancers observed in workers exposed to 1,3-butadiene.

In both rodent species, females are apparently more sensitive than males, as evidenced by the higher risk estimates. The "best estimate" (i.e., MLE from the linear model) of 8.7×10^{-3}/ppm for extra cancer risk from the human (male) leukemia data exceeds the upper bound estimates based on the male rat data and on the male mouse data for lymphocytic lymphomas, and is 25 times lower than the upper bound estimate based on all male mouse tumors.

Human health risk estimates based on extrapolation from high-quality epidemiologic results are preferable to those based on rodent data because they avoid the uncertainties inherent in extrapolating across species and, typically, the human exposures in epidemiologic studies are closer to anticipated environmental exposures than the high exposures used in animal studies, thus reducing the extent of low-dose extrapolation. In the case of 1,3-butadiene, while the rat exposures were far in excess of human exposures, the lowest EXPOSURE in the 1993 NTP mouse study (4.7 ppm, 8 h TWA) is within the range of occupational exposures (0.7-1.7 ppm median and 39-64 ppm max 8 h TWAs for work-area groups). However, interspecies differences

in tumor sites and susceptibilities between rats and mice are especially pronounced, and the biological bases for these differences are unresolved. A review of available pharmacokinetic data and models revealed that the state of the science is currently inadequate for either explaining interspecies differences or improving on default dosimetry assumptions. Therefore, the quantitative extrapolation of rodent risks to humans is highly uncertain for 1,3-butadiene.

Even though high-quality human data were used for the quantitative cancer risk estimation for 1,3-butadiene, there are inevitable uncertainties in the calculated risk estimate. *First, there are uncertainties inherent in the epidemiologic study itself.* In particular, there are uncertainties in the retrospective estimation of 1,3-butadiene exposures, which could have resulted in exposure misclassification. Nondifferential exposure misclassification would tend to bias estimates of effect toward the null, resulting in an underestimate of risk. Differential misclassification could bias results in either direction.

Second, there are uncertainties regarding the appropriate dose metric for dose-response analysis. Although the dose surrogate of cumulative exposure (i.e., ppm × years) yielded highly statistically significant exposure-response relationships, cumulative exposure is strongly correlated with other possible exposure measures, and there may be a dose-rate effect (e.g., risk at high exposures may be more than proportionately greater than at lower exposures) obscured in the analysis, or operative at exposures below the observable range but relevant to low-dose extrapolation.

Third, there are uncertainties pertaining to the model for low-dose extrapolation. Although Delzell et al. expressed preference for the square root model based on its goodness of fit, the four exposure-response models that they investigated were virtually indistinguishable on statistical grounds, and because the specific mechanisms of 1,3-butadiene carcinogenesis are unknown, there is no biological basis for choosing one model over another. Even though the models give similar results in the observable range, they deviate substantially at lower exposures. For example, at a lifetime continuous exposure of 1 ppb, the preferred model of Delzell et al. yields a cancer potency estimate almost two orders of magnitude higher than that obtained by the linear model. However, there was no apparent biological reason to depart from a default assumption of linearity, so the linear model was used in this risk assessment.

Fourth, it is uncertain which potential modifying or confounding factors should be included in the model. The linear model of Delzell et al., which was used in this risk assessment, adjusted for age, calendar year, years since hire, race, and exposure to styrene. However, these investigators dropped styrene and race from their preferred square root model to obtain their final model. Furthermore, there may be other relevant factors that weren't included in the models at all.

Fifth, there are uncertainties in the parameter estimates used in the models. The study of Delzell et al. is large, providing some degree of reliability in the parameter estimates; however, especially given the large human variability that has been observed in metabolic activities that could affect cancer risk from 1,3-butadiene exposure, the generalizability of the occupational results is unclear.

In addition, there are important concerns raised by comparison with the rodent data. First, the rodent studies suggest that 1,3-butadiene is a multi-site carcinogen. It is possible that humans may also be at risk of 1,3-butadiene-induced carcinogenicity at other sites and that the epidemiologic study had insufficient power to detect the other excess risks. In the mouse, for example, the lung is the most sensitive tumor site. Significant excesses of lung cancer may not have been detectable in the epidemiologic study because of the high background rates of lung cancer in humans. Delzell et al. did observe a slight increase in lung cancer among maintenance workers. The reported excess cancer risk estimate, which is based only on leukemias, may be an underestimate if other sites are also at risk.

Second, both the rat and mouse studies suggest that females are more sensitive to 1,3-butadiene-induced carcinogenicity than males, and the mammary gland in females was the only tumor site common to both species. If female humans are also more sensitive than males, then the male-based risk estimates calculated from the epidemiology study would underestimate risks to females.

Despite these uncertainties, confidence in the excess cancer risk estimate of 9 × 10^{-3}/ppm is relatively high. First, the estimate is based on human data. Furthermore, these data are from a large, high-quality epidemiologic study in which 1,3-butadiene exposures were estimated for each individual *a priori* to conducting the exposure-response analysis. Although there are uncertainties in the exposure estimation, a serious attempt was made to reconstruct historical exposures for specific tasks and work areas. It is virtually unprecedented to have such a comprehensive exposure assessment for individual workers in such a large occupational epidemiologic study. In addition, the assumption of linearity for low-dose extrapolation is reasonable given the clear evidence of genotoxicity by 1,3-butadiene metabolites.

Using the cancer potency estimate of 9×10^{-3}/ppm, the chronic (70 year) exposure level resulting in an increased cancer risk of 10^{-6} (i.e., one in a million) can be estimated as follows: $(10^{-6})/(9 \times 10^{-3}/\text{ppm}) = 1 \times 10^{-4}\text{ppm} = 0.1$ ppb.

11.5. SUMMARY OF REPRODUCTIVE/DEVELOPMENTAL EFFECTS

A variety of reproductive and developmental effects have been observed in mice and rats exposed to 1,3-butadiene by inhalation. There are no human data on reproductive or developmental effects.

The most sensitive developmental endpoint was decreased fetal weight in the mouse. Decreases were observed at the lowest exposure concentration (40 ppm, 6 h/day, gestation days 6-15); thus there was no NOAEL for this effect. Generally, however, it is thought that there is an exposure threshold, and while effects on fetal growth in humans cannot be ruled out, they are not expected to occur from low environmental exposures to 1,3-butadiene. No developmental toxicity was observed in rats.

The most sensitive reproductive endpoints observed in subchronic exposure studies were litter size at birth and at weaning in dominant lethal studies of mice (i.e., male mice are exposed to 1,3-butadiene and effects on litters are measured after mating to unexposed females). Litter size at birth reflects both decreased implants and increased fetal deaths, while litter size at weaning also reflects neonatal deaths. Dominant lethal effects in humans would likely be manifested as spontaneous abortions, miscarriages, stillbirths, or very early deaths. The dominant lethal responses are believed to represent a genotoxic effect; however, a large number of sperm would have to be affected to result in any meaningful increase in risk, because the chances of any single sperm both having a critical mutation and fertilizing an egg are minuscule. Thus, dominant lethal effects are not expected in humans exposed to low environmental exposures, although the possibility of such effects or of transmissible genetic mutations cannot be ruled out.

From chronic exposure studies (2-year bioassays), the most sensitive reproductive effects were ovarian atrophy in female mice and testicular atrophy in male mice. Testicular atrophy was primarily a high-exposure effect and likely has an exposure threshold. Ovarian atrophy, on the other hand, was observed at the lowest exposure level (6.25 ppm, 6 h/day, 5 days/week, for 2 years), although an exposure threshold is assumed for this endpoint as well. Uterine atrophy was also observed in the highest exposure groups: however, this is thought to be a secondary effect of the ovarian atrophy. The mechanisms of ovarian atrophy are unknown, although there is strong evidence that the effect is mediated by the diepoxide metabolite. It is further expected, based on metabolic data, that humans would produce lower concentrations of this metabolite than do mice. Thus, it is likely that humans are less sensitive to 1,3-butadiene-induced ovarian atrophy than are mice. No reproductive effects were reported in the 2-year rat study. In conclusion, ovarian atrophy is not expected in humans from environmental exposures to 1,3-butadiene; although, the effect cannot be ruled out.

11.6. QUANTITATIVE ESTIMATION (RfC) FOR REPRODUCTIVE/ DEVELOPMENTAL EFFECTS

An RfC for reproductive and developmental effects of 0.15 ppb was obtained for the critical effect of decreased litter size at birth (or at weaning), based on subchronic dominant lethal studies in the mouse.

A reference concentration (RfC) is an estimate of the daily exposure to humans that is "likely to be without appreciable risk of deleterious [noncancer] effects during a lifetime." The RfC is calculated for the "critical [noncancer] effect," i.e., the effect for which an increased response is observed at the lowest concentration used in the study, or for which benchmark concentration modeling yields the lowest EC_{10}. In this assessment, the RfC is only for reproductive and developmental effects (R/D RfC), because other noncancer effects were not considered. Of the 1,3-butadiene reproductive/developmental effects, the critical effect was decreased litter size at birth or at weaning (both of these effects yielded the same EC_{10}), as observed in dominant lethal studies of male mice. An R/D RfC was calculated based on the LEC_{10}, which was calculated using benchmark concentration methodology, and uncertainty factors for interspecies extrapolation (3), intraspecies variability (10), extrapolation from subchronic study to chronic exposure (3), the absence of multigenerational studies (3), and "risk reduction" to extrapolate to a level at which no detectable effects are expected (analogous to the LOAEL-to-NOAEL uncertainty factor) (3). The resulting R/D RfC is 0.15 ppb [0.15 ppm/(3×10×3×3×3)]. The actual risks at low exposure levels are unknown; the R/D RfC merely provides a bound on chronic exposure below which no "appreciable risk" of reproductive or developmental effects is expected.

Although other noncancer effects were not examined, the reproductive endpoints were quite sensitive, and it is likely that the R/D RfC is protective against other noncancer effects as well.

In addition, a RfC_{DT} of 0.1 ppm for developmental toxicity from short-term exposures was calculated from the mouse fetal weight data, and a R/D RfC for subchronic exposures of 0.0015 ppm was derived from the dominant lethal results in mice, each using benchmark concentration methodology to obtain the "point of departure" for applying uncertainty factors.

11.7. SPECIAL SUBPOPULATIONS

11.7.1. Sensitive Subpopulations

It is uncertain whether children or other subpopulations have greater susceptibility to exposure to 1,3-butadiene than the general population.

There is no information available on health effects in children from exposure to 1,3-butadiene at this time. Occurrence of leukemia is causally associated with exposure to 1,3-butadiene in adults, and leukemia is one of the most common cancers in children. Furthermore, leukemia risk in children has been shown to increase with simultaneous exposure to multiple risk factors (Gibson et al., 1968). Thus, exposure to 1,3-butadiene may be an additional risk factor increasing the leukemia risk further in children.

Tobacco smoke contains 1,3-butadiene as well as other carcinogens, and there are a few studies suggesting that parental smoking increases the risk of leukemia or lymphoma in children (John et al., 1991; Stjernfeldt et al., 1986). The overall evidence, however, is inconclusive because other studies observed no increased risk. Furthermore, if there is an effect in children from parental smoking, it is unclear whether it is attributable to preconception effects on fathers' sperm, in utero exposure of the fetus, and/or postnatal exposure to environmental tobacco smoke.

Because metabolic activation of 1,3-butadiene to epoxide metabolites is believed to be necessary for carcinogenicity, it is possible that genetic differences in metabolic or detoxification enzymes could result in different risks to different human subpopulations. For example, investigators have observed that polymorphism in glutathione-S-transferase genes confers differential susceptibility to the induction of sister chromatid exchanges by butadiene metabolites in cultured human lymphocytes. However, the critical/rate-limiting mechanistic steps are unknown at present; thus, it is unknown whether or not there are actual human subpopulations that may have notably different susceptibility to 1,3-butadiene.

11.7.2. Highly Exposed Subpopulations

Some subpopulations may be at greater risk than the general population as a result of higher exposure to 1,3-butadiene.

Heavy smokers may be highly exposed to 1,3-butadiene due to its formation in tobacco smoke. Cigarette smoke has been shown to be a risk factor for various types of leukemias. It should be noted, however, that known and suspected leukemogenic constituents of tobacco smoke include benzene, polonium-210, nitrosamines, and hydrocarbons in addition to 1,3-butadiene (Schottenfeld and Fraumeni, 1996).

11.8. FUTURE RESEARCH NEEDS

Although 1,3-butadiene is classified as a known human carcinogen in this assessment, there are some data gaps in various areas which, if filled, will refine the assessment. The specific research needs are as follows:

Epidemiology

- The medical records for the leukemia cases in the studies by Delzell et al. and Macaluso et al. should be reviewed to verify the cell types of leukemias.
- Further follow-up of these studies is recommended because it will give an opportunity to observe whether any noncancer effects, such as cardiovascular, or any cancers with a longer latency period are associated with exposure to 1,3-butadiene.

- Studies in other polymer facilities around the world could also add to the human evidence of carcinogenicity.

- All epidemiologic studies to date have examined male cohorts. Some butadiene production facilities around the world (e.g., China) employ women in their laboratories. If the number of women in these facilities is large enough, a reproductive/developmental study would help determine if female workers are at risk of reproductive effects or if exposed fetuses are at risk of developmental effects.

- A reproductive study of exposed males is also needed to examine potential dominant lethal effects in humans.

Toxicology

- Elucidation of the mechanisms responsible for the interspecies differences in sensitivity to 1,3-butadiene could assist in resolving questions about the human risk for reproductive effects and for cancer at sites for which the Delzell et al. study may have had insufficient power to detect an effect.

Molecular biology

- Once the mechanisms of 1,3-butadiene-induced health effects are better understood, information on polymorphisms in human metabolic enzymes (or DNA repair enzymes, etc.) could help define sensitive subpopulations.

11.9. SUMMARY AND CONCLUSIONS

The purpose of this effort was to review the new information that has become available since EPA's 1985 health assessment of 1,3-butadiene and to determine if any changes were needed to the earlier conclusions.

1,3-Butadiene is a gas used commercially in the production of styrene-butadiene rubber, plastics, and thermoplastic resins. The major environmental source of 1,3-butadiene is the incomplete combustion of fuels from mobile sources (e.g., automobile exhaust). Tobacco smoke can be a significant source of 1,3-butadiene in indoor air.

This assessment concludes that 1,3-butadiene is a *known human carcinogen*, based on three types of evidence: (1) epidemiologic studies showing increased leukemias in workers occupationally exposed to 1,3-butadiene (by inhalation), (2) studies showing that 1,3-butadiene causes a variety of tumors in mice and rats by inhalation, and (3) studies demonstrating that 1,3-butadiene is metabolized into genotoxic metabolites by experimental animals and humans. The specific mechanisms of 1,3-butadiene-induced carcinogenesis are unknown; however, it is virtually certain that the carcinogenic effects are mediated by genotoxic metabolites of 1,3-butadiene.

The best estimate of human lifetime extra *cancer risk* from chronic exposure to 1,3-butadiene is 9×10^{-3} *per ppm* based on linear modeling and extrapolation of the increased

leukemia risks observed in occupationally exposed workers. Although there is uncertainty in extrapolating from occupational exposures to lower environmental exposures, this risk estimate has the advantage of being based on a large, high-quality *human* study, and linear extrapolation is warranted by the known genotoxicity of 1,3-butadiene metabolites. The corresponding estimate of the chronic exposure level of 1,3-butadiene resulting in an extra cancer risk of 10^{-6} (i.e., one in a million) is 0.1 ppb. The 95% upper bound on unit risk from the linear model is 0.02/ppm.

1,3-Butadiene also causes a variety of reproductive and developmental effects in mice and rats; no human data on these effects are available. The most sensitive effect was reduced litter size at birth and at weaning observed in studies in which exposed male mice were mated with unexposed females. In humans, such an effect might be manifested as an increased risk of spontaneous abortions, miscarriages, stillbirths, or very early deaths. Based on this critical effect of reduced litter size, a reference concentration (i.e., a chronic exposure level presumed to be "without appreciable risk") of 0.15 ppb for reproductive and developmental effects was calculated from the modeled benchmark concentration (LED_{10}) of 0.15 ppm. The actual risks at low exposure levels are unknown; this RfC merely provides a bound on chronic exposure below which no "appreciable risk" of reproductive or developmental effects is expected.

There are insufficient data from which to draw any conclusions on potentially sensitive subpopulations.

In summary, the primary changes in EPA's conclusions about the health effects of 1,3-butadiene from the 1985 document to this one are:

- The cancer classification has been changed from probable to known human carcinogen.

- The unit cancer risk estimate has been changed from 0.25/ppm (upper bound based on mouse data) to 0.009/ppm (best estimate based on linear modeling and extrapolation of human data).

- For the first time, an RFC (0.15 ppb) is calculated for reproductive/developmental effects.